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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,250	01/06/2006	Marc K Hellerstein	416272003800	8807
	7590 02/03/200 FOERSTER LLP	9	EXAMINER	
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SAN FRANCISCO, CA 94105-2482			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(s)				
Office Action Summary	10/523,250	HELLERSTEIN, MARC K				
Office Action Cummary	Examiner	Art Unit				
	MARCELA M. CORDERO GARCIA	1654				
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply						
A SHORTENED STATUTORY PERIOD FOR REPL' WHICHEVER IS LONGER, FROM THE MAILING D. - Extensions of time may be available under the provisions of 37 CFR 1.1 after SIX (6) MONTHS from the mailing date of this communication. - If NO period for reply is specified above, the maximum statutory period of Failure to reply within the set or extended period for reply will, by statute Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	ATE OF THIS COMMUNICATION 36(a). In no event, however, may a reply be tir will apply and will expire SIX (6) MONTHS from the cause the application to become ABANDONE	N. nely filed the mailing date of this communication. ED (35 U.S.C. § 133).				
Status						
1) Responsive to communication(s) filed on <u>22 S</u>	eptember 2008.					
3) Since this application is in condition for allowa	3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is					
closed in accordance with the practice under E	Ex parte Quayle, 1935 C.D. 11, 4	53 O.G. 213.				
Disposition of Claims						
4)⊠ Claim(s) <u>1-47</u> is/are pending in the application.						
4a) Of the above claim(s) <u>46 and 47</u> is/are withdrawn from consideration.						
5) Claim(s) is/are allowed.						
6)⊠ Claim(s) <u>1-45</u> is/are rejected.						
7) Claim(s) is/are objected to.						
8) Claim(s) are subject to restriction and/or election requirement.						
Application Papers						
9)☐ The specification is objected to by the Examine	r.					
10)☐ The drawing(s) filed on is/are: a)☐ accepted or b)☐ objected to by the Examiner.						
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).						
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).						
11)☐ The oath or declaration is objected to by the Ex	caminer. Note the attached Office	Action or form PTO-152.				
Priority under 35 U.S.C. § 119						
12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of:						
1. Certified copies of the priority documents have been received.						
2. Certified copies of the priority documents have been received in Application No						
3. Copies of the certified copies of the priority documents have been received in this National Stage						
application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received.						
oco the attached detailed Office action for a list of the certified copies hot received.						
Attachment(s)						
1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413)						
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail D	Paper No(s)/Mail Date				
3) Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/05,5/05,1/06,5/06,10/06,6/07,7/07,11/07,8/08. 5) Notice of Informal Patent Application 6) Other:						

DETAILED ACTION

Claims 1-47 are pending in the application.

Election/Restrictions

Applicant's election of Group I, claims 1-45 in the reply filed on 6/3/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Additionally, with regards to the election of species: Applicant has elected ²H as the isotope label, H₂O as the organic metabolite or organic metabolite precursor to said cell, and a "therapeutic agent" as the "therapeutic or diagnostic agent" to be administered.

Claims 1-45 are presented for examination. Claims 46-47 are withdrawn as not drawn to the elected group.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (US 6,764,817; citation 15, IDS of 01/06) in view of Papageorgopoulos (Anal Biochem 1999; citation 6, IDS of 01/05) and Hellerstein (Faseb Abstracts 2002; citation 121, IDS Of 05/05).

Schneider et al. teach a method for determining the molecular flux rates of a plurality of proteins in all or a portion of the proteome of a cell, tissue or organism, said method comprising:

- a) administering one or more isotope-labeled protein precursors to said cell, tissue or organism for a period of time sufficient for one or more isotope labels to be incorporated into a plurality of proteins in the proteome or portion thereof of the cell, tissue or organism [e.g., col. 12, lines 20-67 and cols. 13-15];
- b) obtaining the proteome or portion thereof from the cell, tissue or organism [e.g., col. 15, lines 38-67; col. 16];
- c) identifying a plurality of mass isotopomeric envelops of ions representing individual proteins in the proteome or portion of the proteome by mass spectrometry [i.e., col. 21 lines 30-60];
- d) quantifying relative mass isotopomer abundances of ions within the mass isotopomeric envelope corresponding to each identified protein by mass spectrometry; [e.g., column 21, lines 30-60] and
- e) calculating the molecular flux rates of each identified protein to determine the molecular flux rates of said plurality of proteins [e.g., col. 22, lines 58-67; col. 23-24].

Schneider et al. teach a method to determine metabolite concentration and/or flux, with purifying and detection methods which enable one to determine how various parameters for metabolites of interest (e.g., metabolite concentration and/or flux) vary as a function of different cellular states or exposure to different stimuli. Once correlation has been established, certain methods of the invention can be utilized to screen for

particular states (e.g., col. 4). Such correlations have the potential to provide significant insight into the mechanism of disease, cellular development and differentiation, as well as in the identification of new therapeutics, drug targets and/or disease markers, i.e., diagnostic agents (e.g., col. 1, lines 25-35). Schneider teach the administration of the isotope-labeled protein precursors which can be administered orally, aerosol, parenterally, intravenous, intradermally, topically, intravesically, intrathecally. When the protein precursor is administered to a portion of cells, the cells can be suspended in a matrix containing the isotopically-enriched substrate (see cols. 14-15). Administration includes pulsed additions (e.g., cols. 13-14).

What is missing in Schneider et al. is the quantification of the absolute mass isotopomer abundances of ions at the time of measuring the concentration of the encriched stable isotope [e.g., column 21, lines 30-60]. However, Schneider does teach that the measurement of the concentration of the enriched stable isotope can be made according to a variety of options [e.g., col.21, lines 40-42, cols. 21-24].

Papageorgopoulos et al. teaches the measurement of molecular flux by isotopic techniques wherein the measurement encompasses:

- d) quantifying relative and absolute mass isotopomer abundances of ions with the mass isotopomeric envelope corresponding to an identified protein [e.g., pages 5-8]
- e) calculating the molecular flux rates of the identified protein to determine the molecular flux rate of said protein [e.g., pages 9-16].

What is missing in Papageorgopoulos is the use of ²H₂O as isotope-labeled precursor in the measurement of molecular flux of proteins.

Hellerstein et al. teach measuring of synthesis rates of slow-turnover proteins from $^2\text{H}_2\text{O}$ incorporation into non-essential amino acids (NEAA) and application of mass isotopomer distribution analysis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Schneider et al. by utilizing measurement methods as taught by Papageorgopoulos et al. and Hellestein et al. The skilled artisan would have been motivated to do so in order to express the full scope of metabolic measurements within the proteome given that the Schneider et al. method is based on determination of metabolite concentration and/or flux, with purifying and detection methods which enable one to determine how various parameters for metabolites of interest (e.g., metabolite concentration and/or flux) vary as a function of different cellular states or exposure to different stimuli. Once correlation has been established, certain methods of the invention can be utilized to screen for particular states (e.g., col. 4). Such correlations have the potential to provide significant insight into the mechanism of disease, cellular development and differentiation, as well as in the identification of new therapeutics, drug targets and/or disease markers, i.e., diagnostic agents (e.g., col. 1, lines 25-35). There would have been a reasonable expectation of success because Schneider et al. taught that the measurement of the molecular fluxes could be done using other techniques / calculations [e.g., col.21, lines 40-42, cols. 21-24].

Schneider et al. teach: the limitation of claims 2 and 27: "continuous" is taught, e.g., in col. 15, lines 30-37. The limitation of claims 3 and 28: "regular measured intervals" is taught, e.g., in paragraph bridging cols. 13-14. The limitation of claims 5

and 29: "orally" is taught, e.g., in col. 14, lines 14-64. The limitation of claim 6: "modifying said proteins prior to said measuring step" is taught, e.g., col. 13, lines 5-25. The limitation of claim 6: "biochemically degrading" and the limitation of claim 7: "chemically altering" is taught, e.g., in col.16. The limitation of claim 7: "chromatography" is taught, e.g., in col. 16. The limitations of claims 8-9: "proteome" is taught, e.g., in col. 1-3. The limitation of claim 10: "step of displaying the rates of synthesis and degradation" is taught, e.g., in col. 2, lines 7-9, col. 5, lines 15-35. The limitation of claim 11: "comprise an amino acid" is taught, e.g., in col. 13, lines 1-10 and col. 24. lines 30-45 The limitation of claims 12 and 35: "H₂O, CO₂, NH₃ and HCO₃" is taught, e.g., col. 22, lines 28-35. The limitation of claim 14-15 and 25-26: "2H" is taught, e.g., in column 13, lines 5-35 and col. 24, lines 20-45. The limitation of claims 14 and 26: "amino acid" is taught, e.g., in col. 13, lines 5-10 and col. 24, lines 30-45. The limitation of claims 17 and 40: "human" is taught, e.g., in col. 12, lines 50-67. The limitation of claim 18: "discontinuing" is taught, e.g., in cols. 13-14. The limitation of claim 19: "administering a diagnostic or therapeutic agent" is taught, e.g., in column 1, lines 25-35. The limitation of claims 20-21 and 42-43 "determining the effect of a diagnostic or therapeutic agent" is taught, e.g., col. 1, lines 25-35. The limitation of claim 23: "isolating" is taught, e.g., in cols. 16-21. Hellerstein et al. teach the limitation of claims 16 and 37-39 "H₂O" in, e.g., abstract. The limitation of claim 41: "administering prior to said administering step (a) is not expressly taught. The limitation of claim 44: "effects of one or more genes on the molecular flux" is taught, e.g., in col. 2, last par.

and col. 3. The limitation of claim 45: "isolating a plurality of samples from said cell,

tissue or organism is taught, e.g., in cols 4-5 and 15-19. The adjustment of particular conventional working conditions (e.g., administering a therapeutic agent before administering the isotopic label, in order to study its effect on the metabolic turnover; chemically or biochemically modifying the metabolites within such method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. order of administration of therapeutic agents, chemical and biochemical manipulation of metabolites), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". In re-Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in such method to obtain the most accurate, sensitive and versatile method. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-15, 17-36, 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (US 6,764,817; citation 15, IDS of 01/06) in view of Aebersold et al. (US 6,670,194).

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Schneider et al. is relied upon as above.

What is missing in Schneider et al. is the quantification of the absolute mass isotopomer abundances of ions at the time of measuring the concentration of the encriched stable isotope [e.g., column 21, lines 30-60]. However, Schneider does teach that the measurement of the concentration of the enriched stable isotope can be made according to a variety of options [e.g., col.21, lines 40-42, cols. 21-24].

Aebersold et al. teach a method for rapid, quantitative analysis of proteins complex mixtures. The method provides quantification of the levels of specific isotopically labeled proteins in multiple samples in a single analysis. The method also provides for qualitative and quantitative measurement of specific proteins in biological fluids, cells or tissues and can be applied to determine global protein expression profiles in different cells and tissues. The same general strategy can be broadened to achieve the proteome wide, qualitative and quantitative analysis of the state of modification of proteins (e.g., abstract, cols. 1-7). Aebersold et al. teach Quantitative relative amounts of proteins in one or more different samples containing protein mixtures (e.g., biological fluids, cell or tissue lysates, etc.) can be determined using chemically identical, affinity tagged and differentially isotopically labeled reagents to affinity tag and differentially isotopically label proteins in the different samples. In this method, each sample to be compared is treated with a different isotopically labeled

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reagent to tag certain proteins therein with the affinity label. The treated samples are then combined, preferably in equal amounts, and the proteins in the combined sample are enzymatically digested, if necessary, to generate peptides. Some of the peptides are affinity tagged and in addition tagged peptides originating from different samples are differentially isotopically labeled. As described above, affinity labeled peptides are isolated, released from the capture reagent and analyzed by (LC/MS). Peptides characteristic of their protein origin are sequenced using MS.sup.n techniques allowing identification of proteins in the samples. The relative amounts of a given protein in each sample is determined by comparing relative abundance of the ions generated from any differentially labeled peptides originating from that protein. The method can be used to assess relative amounts of known proteins in different samples. Further, since the method does not require any prior knowledge of the type of proteins that may be present in the samples, it can be used to identify proteins which are present at different levels in the samples examined. More specifically, the method can be applied to screen for and identify proteins which exhibit differential expression in cells, tissue or biological fluids. It is also possible to determine the absolute amounts of specific proteins in a complex mixture. In this case, a known amount of internal standard, one for each specific protein in the mixture to be quantified, is added to the sample to be analyzed. The internal standard is an affinity tagged peptide that is identical in chemical structure to the affinity tagged peptide to be quantified except that the internal standard is differentially isotopically labeled, either in the peptide or in the affinity

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tag portion, to distinguish it from the affinity tagged peptide to be quantified. The internal standard can be provided in the sample to be analyzed in other ways. For example, a specific protein or set of proteins can be chemically tagged with an isotopically-labeled affinity tagging reagent. A known amount of this material can be added to the sample to be analyzed. Alternatively, a specific protein or set of proteins may be labeled with heavy atom isotopes and then derivatized with an affinity tagging reagent. Aebersold et al. therefore teach chemical and biochemical modification of the proteins from different samples and then using mass spectrometry for detection of relative and absolute abundance, e.g, Table 5, cols. 51-52 and Scheme 1 as in the limitation of instant claims 6-8: "biochemically degrading" and "chemically altering".

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Schneider et al. by utilizing relative and absolute abundance measurements as taught by Aebersold et al. which taught, as Schneider et al., a proteomic analysis mass spectrometric method (e.g., abstract, and col. 5-6) including detection of proteins. The skilled artisan would have been motivated to do so in order to express the full scope of metabolic measurements possible within the proteome protein and metabolite detection method of Schneider et al. in order to determine flux in metabolites of interest (e.g., metabolite concentration and/or flux) vary as a function of different cellular states or exposure to different stimuli. There would have been a reasonable expectation of success because Schneider et al. taught that the measurement of the molecular fluxes could be done using other techniques / calculations [e.g., col.21, lines 40-42, cols. 21-24]. The adjustment of particular

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conventional working conditions (e.g., administering a therapeutic agent before administering the isotopic label, determining absolute and relative mass isotopomer abundances within such method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. order of administration of therapeutic agents, determination of relative and absolute mass isotopomer abundances within such method), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in such method to obtain the most accurate, sensitive and versatile method. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-21 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As discussed in the Guidelines for Examination of Patent Applications under the 35 USC 112, paragraph 1, "Written Description", examination of patent claims for compliance with the Written Description Requirement should include (http://www.uspto.gov/web/menu/written.pdf):

1. A determination as to what the claim as a whole covers. In making this determination, the examiner should consider the full scope of the claim.

In the instant case the claims are drawn to a method for determining the effect of a diagnostic or therapeutic agent on a cell wherein said effect is used for the discovery, development or approval of a drug or other therapeutic agent (claims 20-21) and a method for determining the effect of any diagnostic or therapeutic agent on a cell, tissue or organism to use for the discovery, development or approval of a drug or other therapeutic agent (claims 42-43). The scope is extremely broad, including any therapeutic agent and any diagnostic agent, any effect thereof in any tissue, cell, or

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organism and it extends to the discovery, development or approval of a drug or other therapeutic agent.

2. A full review of the application to understand how the applicant provides support for the claimed invention including each element and/or step. This review includes comparing the claim scope with the scope of the description.

In the instant case, the disclosure does teach that the kinetic measurements allow direct inference of regulatory steps controlling homeostasis of the proteome and organeome and that labeling the proteome has up to two orders of magnitude greater than static measurements for detecting treatment effects (i.e., < 200 proteins out of 20,000 show large changes in static concentrations at steady state after even the most potent interventions, whereas up to 40-50% of proteins show large changes in synthetic or catabolic rates at steady state after potent intervention [0153]-[0160] of the instant application publication.

3. A determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing.

The determination should include the following considerations:

- a. Actual reduction to practice.
- b. disclosure of drawings or structural chemical formulas.
- c. Sufficient relevant identifying characteristics such as;
 - i. Complete structure
 - ii. Partial structure
 - iii. Physical and/or chemical properties

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iv. Functional characteristics when coupled with a know or disclosed correlation between function and structure

- d. Method of making the claimed invention
- e. Level of skill and knowledge in the art
- f. Predictability in the art

In the instant case, the level of skill is high and the knowledge in the art is low, since screening for whole proteome or organeome effects is a complex process which is not highly predictable. In addition to the level of unpredictability of such bioanalytical method which involves using any therapeutic or diagnostic agent, any protein or metabolic precursor labeled with isotopes in order to find medication/drug/diagnostic agents and extend it to the discovery, development or approval of such drug or therapeutic agent. Moreover, not a single working Example is provided

4. For each claim drawn to a single embodiment or species, consider the above factors in regard to that embodiment or species to determined whether one of ordinary skill in the art would recognize that the applicant was in possession of the species or embodiment at the time of filing.

In the instant case the claims are drawn to a genus of methods (see step 5).

5. For each claim drawn to a genus, consider each of the above factors to determine whether there is disclosure of a representative number of species which would lead one skilled in the art to conclude that the applicant was in possession of the claimed invention. The number of species required to represent a genus will vary, depending on the level of skill and knowledge in the art and the variability among the

claimed genus. For instance, fewer species will be required where the skill and knowledge in the art is high, and more species will be required where the claimed genus is highly variable.

In the instant case, there are no species provided for the highly variable genus of methods for determining the effect of any drug or diagnostic agent which would lead to the discovery, development or approval of such drug or therapeutic agent. One skilled in the art would not recognize possession of the invention at the time of filing.

Therefore, based on the analysis above, it is deemed that no sufficient written description has been provided for the claims above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-7 recite the limitation "prior to said measuring step" in lines 1-2. There is insufficient antecedent basis for this limitation in claim 5 and dependent claims 6-7.

Claim Objections

Claims 18 and 30 are objected to because of the following informalities: The claims are drawn to "comprising the additional step of discontinuing said administering step (a)". However, the claims are unclear as to when and where is the discontinuing happening, especially since step (a) is essential to the claim on which claim 18 depends. The disclosure was examined for clarification on these claims, [0011] and

[0020] of the publication of the application. However, the disclosure is limited to an identical statement as the claims, hence does not provide any further enlightenment with regards to the claims above. Appropriate correction is required.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/ Supervisory Patent Examiner, Art Unit 1654 /Marcela M Cordero Garcia/ Examiner, Art Unit 1654

MMCG 01/09